

VACCINIUM VITIS-IDAEA, A MEDICINAL PLANT OF THE JAMES BAY CREE WITH PROMISING ANTIDIABETIC PROPERTIES: ELUCIDATION OF ITS MECHANISM OF ACTION AND IDENTIFICATION OF ACTIVE PRINCIPLES

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As a part of an ongoing project aiming to develop culturally-adapted diabetes treatment for Canadian native populations, our team has identified several medicinal plants that possess promising antidiabetic potential from among species used by the Cree of Eeyou Istchee (James Bay area of northern Quebec) to treat symptoms related to diabetes (Leduc et al., 2006; Spoor et al., 2006, Harbilas et al., 2009). One of these plants, *Vaccinium vitis idaea*, was recently identified for its capacity to enhance C2C12 skeletal muscle glucose uptake *in vitro* (Harbilas et al., 2009). The goal of this study was to elucidate the mechanism of action of the berries of *V. vitis* as well as to isolate and identify its active constituents. C2C12 cells were treated with crude ethanol extract of *V. vitis* berries for 18 hours and insulin-dependent and -independent signalling pathways examined. Western immunoblot analysis revealed that the ethanol extract of the berries did not stimulate the protein kinase Akt (a key component of insulin signaling pathways). Instead, *V. vitis* berry extract activated the enzyme acetyl co-A carboxylase (ACC), a reliable marker of the AMP-activated protein kinase (AMPK) pathway; AMPK being a master metabolic switch that is also the target of metformin, the most commonly prescribed oral hypoglycaemic drug. The extract was also observed to mildly inhibit ADP-stimulated oxygen consumption in isolated liver mitochondria, an effect likely responsible for metabolic stress and for the ensuing activation of the AMPK-ACC cascade. Fractionation guided by radiolabelled glucose uptake activity resulted in the isolation of 9 compounds. The 3 most active, quercetin, quercetin-3-O-galactoside and quercetin-3-O-glucoside, enhanced glucose uptake by $37\pm 9\%$, $59\pm 2\%$ and $38\pm 4\%$, respectively, after an 18 hour treatment, as compared to $31\pm 7\%$ for the crude berry extract. These flavonoid glycosides, as well as the aglycone, were observed to stimulate the AMPK pathway in the dose range of 50 to 100 μM . Quercetin was a powerful inhibitor of ATP synthase in isolated mitochondria. These findings indicate that quercetin and its glycosides likely participate in the antidiabetic activity of *V. vitis* crude berry extract mediated by AMPK. Crude preparations of *V. vitis* berries, as well as the flavonoids quercetin and quercetin-3-glycosides thus potentially have applications for the prevention and treatment of metabolic diseases.